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Effectiveness and safety of the use of conscious sedation in patients submitted to dental procedures: systematic review – study protocol

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Title: Effectiveness and safety of the use of conscious sedation in patients submitted to dental procedures: systematic review – study protocol

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ABSTRACT

Introduction: The management of patients with anxiety undergoing dental procedures is still a challenge in clinical practice. Dental surgeons have doubts regarding the effectiveness and safety of drugs used for conscious sedation. This study will evaluate the effectiveness and safety of the use of conscious sedation with benzodiazepines and other agents orally administered in patients undergoing dental surgical procedures.

Method/Design: We will conduct a systematic review and, if appropriate, a meta-analysis of randomized controlled clinical trials that will evaluate the use of conscious sedation administered by oral route in adult patients undergoing dental surgical procedures. The search will be conducted using electronic databases, such as the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via Ovid); EMBASE (via Ovid); CINAHL (via Ovid); Lilacs (Scielo); and Capes database, without restriction in languages or date of publication. Primary outcomes include anxiety, sedation, treatment satisfaction, pain and adverse effects; secondary outcomes include vital parameters (heart rate, respiratory rate, and blood pressure) and patient cooperation during intervention. A team of reviewers will independently assess each citation for eligibility and in duplicates. For eligible studies, the same reviewers will perform data extraction, bias risk assessment, and determination of the overall quality of evidence for each of the outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) classification system.

Ethics and Dissemination: The evidence of this study will allow dentists to know about the efficacy and safety of the use of conscious sedation orally in patients requiring dental surgical procedures and would thus help in decision-making process in clinics in order to minimize the risks of anxiety and pain in the dental practice, as well as possible effects. Updates of this study will be conducted in order to inform and orient clinical practice.

Protocol registration: PROSPERO - CRD42017057142

Strengths and limitations of this study

- Anxiety and risk of adverse effects with the use of sedatives are negative outcomes in dentistry that may interfere with pre, trans, and post treatment effects during surgical interventions at a clinic. To estimate the risk rate of such episodes in patients treated with anxiolytic or sedative intervention may contribute to the decision-making process concerning conscious sedation.
- The use of GRADE will evaluate the strength and quality of the body of evidence regarding the estimate of the effect for each outcome, including independent analysis of bias risk, accuracy, consistency, publication bias, and indirect evidence.
- The method of this review includes explicit eligibility criteria, comprehensive and extensive search of databases, independent and duplicate quality evaluation, and study eligibility.
- The quality of the primary studies to be included in this review may be a limiting factor because of the design of each study and the measurement of their outcomes.

INTRODUCTION

The effective control of anxiety and pain is an important factor that influences patient's compliance and adherence to dental treatment. For behavioral management, the use of analgesia and conscious sedation methods are important strategies for treating patients who have anxiety due to dental treatment.[1]

Conscious sedation is a technique that uses one or more drugs in order to produce a state of depression of the central nervous system that retains verbal contact with the patient during the period of sedation.[2] The sedation level must be such that the patient remains conscious and is capable of readily understanding and answering verbal commands or followed by a tactile stimulation.[3]

Indications for the use of conscious sedation as a patient's management tool include presence of anxiety and dental phobia, prolonged or traumatic dental procedures, medical conditions potentially aggravated by stress, and medical conditions that affect the capacity of the patient to cooperate, such as special needs.[4]

There are some non-pharmacological (such as behavioral cognitive therapy, hypnosis, and music therapy) and pharmacological modalities that may contribute to the control of anxiety and facilitate dental treatment. [5 6] Conscious sedation is a pharmacological option in which some drugs present advantages, such as muscle relaxation, anticholinergic effect, rapid onset, and short elimination half-life, which is considered to be an interesting tool.[7]

Drug interventions to provide conscious sedation for dental treatment must have a safety margin large enough so that the loss of consciousness is unlikely to happen.[8]

Benzodiazepines are more commonly administered orally in dentistry, although sublingual and intravenous administration is available.[9 10] In addition to midazolam, other benzodiazepines such as diazepam and alprazolam have been successfully used in conscious sedation.[11 12] Diazepam, alprazolam and midazolam have similar sedative characteristics.[11 13]

Diazepam is rapidly absorbed, has a long half-life and due to it hepatic metabolism produces metabolites with pharmacological activity, such as nordazepam, temazepam and oxazepam.[14] The pharmacokinetic characteristics of midazolam make it the preferred choice. When the safety of midazolam was evaluated, it was observed that complications seem to be transitional. [15] Benzodiazepines have a high therapeutic index and therefore possess a high margin of safety compared with other classes of sedative hypnotics. [16]

Even though there is a great variety of drugs that may be used for conscious sedation in dentistry, there are few studies comparing their effectiveness and safety in adults. Therefore, the aim of this systematic review is to determine whether benzodiazepines and other drug interventions administered orally are effective and safe in controlling anxiety, vital parameters and pain in patients undergoing dental surgical procedures.

METHODS AND ANALYSES

This systematic review will be conducted in accordance to the recommendations specified by the Cochrane Handbook for Intervention Reviews[17]. Evaluation will be performed following the items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement.[18]

Protocol and Registration

Our review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42017057142) (http://www.crd.york.ac.uk/PROSPERO)

Eligibility criteria

Inclusion criteria

Patients: Adult outpatients, both sexes, and those who need to undergo dental surgical procedures, in particular, simple exodontia, surgery with orthodontic indication, removal of radicular remains and third molars, or dental implants after direct exodontia and in grafted areas.

Interventions: Studies that in at least one arm include the use of conscious sedation orally with benzodiazepines or other drugs in selected patients and in the other arm include placebo (same route of its comparator) or other treatment.

Outcomes: Primary outcomes include anxiety, treatment satisfaction, adverse effects and pain; secondary outcomes include vital parameters (heart rate, respiratory rate, and blood pressure) and patient cooperation during intervention.

Design types: Randomized clinical trial

Exclusion criteria

Studies including adults with comorbidities will be excluded.

Search methods for primary studies

Eletronic searches

Studies will be searched using the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), which includes Dentistry & Oral Health Group's Specialized Register; MEDLINE (via Ovid); EMBASE (via Ovid); CINAHL (via Ovid); Lilacs (Scielo); and Capes database, without restriction in language or date of issuance.

Search strategy

The search strategy will be conducted individually by: oral surgery, benzodiazepines, and other drugs will be combined. The search strategy in Ovid Medline is in Appendix 1.

Searching other resources *(non-conventional literature, semi-published literature, and invisible literature)*

For review articles, one of the reviewers will analyze the reference list or citation in the text in order to verify and identify other possible eligible studies for this review. When necessary, main authors and/or pharmaceutical companies involved in the production of the drugs will be contacted for information on additional trials.

Eligibility determination

Four reviewers (RM, CC, LL and NK), working in pairs, will independently screen potentially relevant citations and abstracts and will apply the selection criteria. Full texts of all articles will be obtained in case either reviewer feels they might be eligible. Two reviewers will independently assess the eligibility of each full-text article and resolve disagreements by consensus. In case of duplicate publication, the article with the more complete data will be used.

Kappa statistics will be used to measure agreement between the examiners. Values of kappa between 0.40 and 0.59 have been considered to reflect fair agreement, values between 0.60 and 0.8 reflect good agreement, and values that are 0.75 or more reflect excellent agreement.[18]

Data extraction

The reviewers will use a standardized and pre-tested form to extract data with information on how to extract them. For articles published with abstracts

only or articles lacking important information, an attempt to obtain complete data on methods and results will be made by contacting the authors.

Two reviewers, in duplicates and independently, will be calibrated upon the extraction of three articles, initially, and then, consensus will be reached. This procedure will be conducted until the reviewers are able to extract data in a standardized manner in order to decrease discrepancies.

Risk of bias in individual studies

A modified version for the Cochrane collaboration will be used for assessing the risk of bias.[19-21] Reviewers will independently evaluate the risk of bias for each randomized study according to the following criteria: adequate randomization; allocation concealment; and blindness of patient, health professional, and outcome evaluators; if the outcomes were reported and the unbalance in the characterization measurements of the sample (*baseline)*. Reviewers will attribute options for answers “definitely yes,” “probably yes,” “probably no,” and “definitely no” for each domain, with “definitely yes” and “probably yes” in last analysis, attributing a low risk of bias, and “definitely no” and “probably no” attributing a high risk of bias.[22] Reviewers will work out any diversion discussing them, and a third person will assess the unresolved ones.

Explaining the heterogeneity of evidence

Quality of the evidence analysis

The quality of the evidence will be independently analyzed (confidence in effect estimates) for each of the results with the use of Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[18 23] In the GRADE approach, randomized studies start with low evidence according to one or more of the five categories of limitation: risk of partiality, incoherence, indirect, inaccuracy, and bias of information.

Possible complications for heterogeneity include drug types, doses (superior vs. inferior) with effects bigger than expected with more elevated doses and treatment time (bigger vs. smaller), and doses with effects bigger than expected with longer treatment time; heterogeneity will be investigated in terms of estimates of combined effect, with the use of the chi-square test and I^2

statistic.[24] Heterogeneity will be categorized as 0%–25% (low heterogeneity); 50% (moderate heterogeneity); or 75% (elevated heterogeneity).[21]

Data synthesis

Intervention drug, intervention group, and each outcome of interest will be analyzed. Confidence in the estimates for each group will be determined, and analysis for body of evidence will be conducted for the one with higher confidence. Hypothesis will be examined for which information will be documented in at least 10 studies for the independent variables or at least five studies for the independent categorical variables.

Combined analysis will estimate the risks of negative outcomes as anxiety and adverse effects in the use of oral sedation.

Meta-analysis will be conducted with the use of STATA (version 10.1), and meta-analysis of randomized effect[25] which are conservative with each study, will be used and differences in the error calculation among studies will be used in the analysis. For the studies with dichotomous outcomes, relative risk will be calculated as well as confidence intervals of 95% (CI 95%).

For continuous data, the difference between weighted mean (WMD) and their CI 95% as effect measure will be used. Once WMD is calculated, this value will be contextualized, taking into account, when available, the minimal important difference (MID); the smaller change in the measure is considered to be important for the patient.

If the studies report the same construction, using different instruments of measurement, the standardized mean difference (SMD) will be calculated as sensitivity analysis. SMD expresses the effect of the intervention in units of standard deviation, instead of initial measures units, with the value of SMD, depending on the size of the effect (the difference between the means) and the standard deviation of the results (the inherent variability among the participants). For measures of results that present (MID), this measure will be used to convert SMD to an odd ratio and difference of risk.[26]

In order to facilitate the interpretation of effects of continuous outcome, MID will be substituted, when available for different scales by standard deviation (denominator) in the WMD equation.[27] If a MID estimate is not available, a statistical approach will be used in order to provide an estimate of a proportion

of patients who would benefit from the treatment in all studies[28] Statistical approaches to enhance the interpretation of results of continuous outcomes described herein will be included in the methods. Funnel plots will be created to explore possible biases of publication, when at least 10 studies are found.[29]

Combined estimates will be tested by Z statistics and heterogeneity by Q statistics among the studies analyzed by the chi-square test. When heterogeneity is present, a component of variance due to the inter-study variance will incorporate the calculation of the confidence interval for the estimate. Studies that do not include any of the above data will not be included in the grouped estimate; for such studies, bleeding rates will be summarized descriptively.

Approaches recently developed to deal with dichotomous[30] and continuous[31] results will be executed. These approaches will be applied to results that meet the following criteria: significant effect in treatment is demonstrated and data lost in sufficient number to potentially introduce clinically important bias are reported. The threshold of participant's lost data will be determined for each outcome.

If meta-analysis is not appropriate because of excessive heterogeneity of population, intervention, comparator, outcome or methodology, and summary charts will be developed and a narrative synthesis will be provided.

Summarizing evidence

Results will be presented in evidence profiles, as recommended by the work group GRADE.[32 33] Evidence profiles will provide succinct presentations of the quality of the evidence and magnitude of effects. Evidence profile will be built with the help of a software, GRADEpro (http://ims.cochrane.org/gradepro), in order to include the following seven elements: (1) a list of up to seven important results (desirable and undesirable); (2) a measure of typical load of these results (i.e., control, group, and estimated risk); (3) a measure of the difference between the risks with and without intervention; (4) the greatness regarding effect; (5) number of participants and studies that approach these outcomes, as well as follow-up period; (6) an evaluation of the global confidence in the estimate of effect for each outcome; and (7) comments, which will include MID, when available. In the GRADE approach, randomized studies

start with high-quality evidence, but may be evaluated as low evidence due to one or more of the five limiting categories: risk of partiality, incoherence, indirect, inaccuracy, and biases of information.

DISCUSSION

This review will evaluate the available evidence regarding the efficacy and safety of the use of oral sedation in adult patients undergoing dental surgical interventions, such as exodontia and dental implants, in order to provide estimates of evidence in a complete and consistent manner, using the GRADE approach.[34] Results of this systematic review will help dentists in the decision-making process in clinical practice in order to decide which is the best sedation choice in patients undergoing surgical procedures.

The information compiled regarding the use of conscious sedation by oral route in patients who will require ambulatory surgical intervention aims to provide information to professionals about the effectiveness and safety of pharmacological modes in these interventions; therefore, this would help to facilitate clinical decisions. This study may also identify interest areas for future investigations.

Abbreviations

Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Virtual Health Library (VHL), Grading of Recommendations Assessment, Development, and Evaluation (GRADE), Randomized clinical trial (RCT), 95% confidence interval (95% CI), Weighted Mean Difference (WMD), Minimal Important Difference (MID).

Competing interests

The authors declare that they have no competing interests.

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Contributors

JOA is the principal investigator and led the writing of the manuscript. LCL and RHLM are the project managers, co-investigators and contributed to the writing and revision of the manuscript. CCB, NKA, CCG, JCR, and MFF are co-investigators and contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

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Appendix 1 - Search strategy (Via Ovid)

1. surgery, maxillofacial.mp. or exp Surgery, Oral/
2. operative dentistry.mp. or exp Dentistry, Operative/
3. dentistry, operative.mp. or exp Dentistry, Operative/
4. prosthesis, surgical dental.mp. or Dental Implants/
5. prostheses, surgical dental.mp. or exp Dental Implants/
6. surgical dental prosthesis.mp. or exp Dental Implants/
7. surgical dental prostheses.mp. or exp Dental Implants/
8. dental prosthesis, surgical.mp. or exp Dental Implants/
9. dental prostheses, surgical.mp. or exp Dental Implants/
10. implant, dental.mp. or exp Dental Implants/
11. dental implant.mp. or exp Dental Implants/
12. implants, dental.mp. or exp Dental Implants/
13. dental implants.mp. or exp Dental Implants/
14. procedures, maxillofacial.mp. or exp Oral Surgical Procedures/
15. procedure, maxillofacial.mp. or exp Oral Surgical Procedures/
16. maxillofacial procedure.mp. or exp Oral Surgical Procedures/
17. maxillofacial procedures.mp. or exp Oral Surgical Procedures/
18. exodontics.mp. or exp Surgery, Oral/
19. procedure, oral surgical.mp. or exp Oral Surgical Procedures/
20. oral surgical procedure.mp. or exp Oral Surgical Procedures/
21. surgical procedures, oral.mp. or exp Oral Surgical Procedures/
22. procedures, oral surgical.mp. or exp Oral Surgical Procedures/
23. surgical procedures, oral.mp. or exp Oral Surgical Procedures/
24. oral surgical procedures.mp. or exp Oral Surgical Procedures/
25. oral surgery.mp. or exp Surgery, Oral/
26. maxillofacial surgery.mp. or exp Surgery, Oral/
27. surgery,oral.mp. or exp Surgery, Oral/

28. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. benzodiazepinones.mp. or exp Benzodiazepinones/
30. Benzodiazepinones.mp. or exp Benzodiazepinones/
31. Alprazolam novopharm brand.mp. or exp Alprazolam/
32. novopharm brand of alprazolam.mp. or exp Alprazolam/
33. novo alprazol.mp. or exp Alprazolam/
34. novoalprazol.mp. or exp Alprazolam/
35. novo-alprazol.mp. or exp Alprazolam/
36. Alprazolam pfizer brand.mp. or exp Alprazolam/
37. pfizer brand of alprazolam.mp. or exp Alprazolam/
38. maleate, midazolam.mp. or exp Midazolam/
39. midazolam maleate.mp. or exp Midazolam/
40. midazolam.mp. or exp Midazolam/
41. effect, antianxiety.mp. or exp Anti-Anxiety Agents/
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46. effect, anxiolytic.mp. or exp Anti-Anxiety Agents/
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52. effect,anti-anxiety.mp. or exp Anti-Anxiety Agents/
53. anti anxiety effect.mp. or exp Anti-Anxiety Agents/
54. anti-anxiety effect.mp. or exp Anti-Anxiety Agents/
55. anxiolytics.mp. or exp Anti-Anxiety Agents/
56. drugs, anti-anxiety.mp. or exp Anti-Anxiety Agents/
57. anti anxiety drugs.mp. or exp Anti-Anxiety Agents/

58. anti-anxiety drugs.mp. or exp Anti-Anxiety Agents/
59. minor tranquillizing agents.mp. or exp Anti-Anxiety Agents/
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61. minor tranquilizing agents.mp. or exp Anti-Anxiety Agents/
62. agents, minor tranquilizing.mp. or exp Anti-Anxiety Agents/
63. tranquilizing agents, minor.mp. or exp Anti-Anxiety Agents/
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65. anxiolytic agents.mp. or exp Anti-Anxiety Agents/
66. anti anxiety agents.mp. or exp Anti-Anxiety Agents/
67. agents, anti-anxiety.mp. or exp Anti-Anxiety Agents/
68. anti-anxiety agents.mp. or exp Anti-Anxiety Agents/
69. **29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68**

70. 69 and 28

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review – **PAGE 1**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **NOT APPLICABLE**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number - **PAGE 5**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author **– PAGE 1**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review **– PAGE 11**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments **NOT APPLICABLE**
Support:		
Sources	5a	Indicate sources of financial or other support for the review **– PAGE 11**
Sponsor	5b	Provide name for the review funder and/or sponsor - **NOT APPLICABLE**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **NOT APPLICABLE**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known **– PAGES 3, 4**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) **– PAGE 4**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review **– PAGE 5**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage **– PAGE 6**
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated - **PAGE 6**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **PAGE 6**

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) **PAGES 6, 7**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators **PAGES 7, 8**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications **PAGES 8-10**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **PAGE 5**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis **PAGE 7**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **PAGES 8, 9**
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) **PAGES 8, 9**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **PAGE 10**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **PAGE 9**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting **PAGES 9, 10**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **PAGES 9, 10**

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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BMJ Open

Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: protocol for a systematic review

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ABSTRACT

Introduction: The management of anxious patients undergoing dental procedures is still a challenge in clinical practice. Despite a wide variety of drugs for oral sedation in adult patients, there are relatively few systematic reviews that compare the effectiveness and safety of different drugs administered via this route. This study will evaluate the effectiveness and safety of oral sedation with benzodiazepines and other agents to patients undergoing dental surgical procedures.

Method/Design: We will conduct a systematic review and, if appropriate, a meta-analysis of randomized controlled clinical trials that will evaluate the use of conscious sedation administered orally to adult patients undergoing oral surgery. The search will be conducted using electronic databases, such as the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via Ovid); EMBASE (via Ovid); CINAHL (via Ovid); Lilacs (Scielo); and Capes database, without restriction of languages or date of publication. Primary outcomes include anxiety, sedation, treatment satisfaction, pain and adverse effects; secondary outcomes include vital parameters (heart rate, respiratory rate and blood pressure) and patient cooperation during intervention. A team of reviewers will independently assess each citation for eligibility and in duplicates. For eligible studies, the same reviewers will perform data extraction, bias risk assessment and determination of the overall quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) classification system.

Ethics and Dissemination: The evidence gathered from this study should provide dental surgeons with knowledge on the effectiveness and safety of oral sedation in adults requiring dental surgical procedures. This in turn should contribute towards the decision-making process in dental practice, minimizing the risks of anxiety and ineffective pain control in clinical procedures, as well as possible side effects. Ethics approval is not required in protocols for systematic reviews. The systematic review will be published in a peer-reviewed journal and presented at conferences.

Protocol registration: PROSPERO - CRD42017057142

Strengths and limitations of this study

- Anxiety and risk of adverse effects with the use of sedatives are negative outcomes in dentistry that may interfere with preoperative, intraoperative and postoperative effects relating to surgical interventions in dental practice. Estimating the risk rate of such events in patients treated with oral sedation may contribute to the decision-making process regarding conscious sedation.
- This study will provide a summary on safety for the commonly used oral sedative drugs for conscious sedation in dentistry.
- The quality of the primary studies to be included in this review may be a limiting factor due to heterogeneity in study design and outcome measurements.

INTRODUCTION

Effective control of anxiety and pain plays a pivotal role on patient compliance and adherence to dental treatment. For behavioural management, the use of analgesia and conscious sedation are important strategies for treating patients who suffer from anxiety to dental treatment.[1]

Conscious sedation is an approach that uses one or more drugs to produce a state of central nervous system depression maintaining verbal contact with the patient throughout.[2] The sedation level must be such that the patient remains conscious and is capable of readily understanding and answering verbal commands or tactile stimulation.[3] Drug interventions to provide conscious sedation for dental treatment must have a wide enough safety margin so that loss of consciousness is unlikely to happen.[4] In addition, considering the different methods of sedation and patient profiles in dental care, monitoring procedures and documentation have been recommended.[3,5,6]

Among the different types of sedation in dentistry, oral sedation is a relatively acessible means for dentists to adress patient anxiety when chairside manner alone is insufficient.[6] Moreover, it involves the administration of a relatively large dose of oral sedatives in dental practice, which differs from the

concept of pre medication, which involves self-administration of a small dose of oral sedative to relieve anxiety.[3]

As per any other approach, oral sedation may present some limitations due to the pharmacokinetics relating to the oral route, such as delayed and variable onset of action.[6] Although it may help patients with mild to moderate levels of anxiety, this technique may be not effective in severely anxious patients.[7]

Oral sedation does not guarantee that a dental patient will achieve a state of anxiolysis or will not drift into deeper levels of sedation, nor is it possible to titrate de drug reliably, as per the case of nitrous oxide or intravenous sedation.[7] Furthermore, there is often an additional risk if the professional should need to complement the dose because of variability in absorption and onset of action.[6]

Since sedation is a continuum, it is not always possible to predict how an individual will respond. Therefore, practitioners intending to obtain a given level of sedation should also be able to rescue patients should they become overly sedated.[8]

Indications for the use of conscious sedation as a patient management tool include a diagnosis of anxiety and dental phobia, prolonged or traumatic dental procedures, medical conditions potentially aggravated by stress, and medical conditions that affect the capacity of the patient to cooperate, such as special needs.[9]

Benzodiazepines are the class of drugs most often used in dentistry to induce a state of anxiolysis[10] and are the drugs of choice for oral sedation in several countries,[3,6,7,11] although sublingual and intravenous administration are also available.[12,13] Historically, temazepam has been the drug of choice for oral sedation in dentistry in some countries, but its use has been largely replaced by midazolam.[3]

Although these drugs have a similar mechanism of action, they differ on pharmacokinetic characteristics, which in turn play an important role on selecting the best option to suit an individual patient's profile [5]. Among the different options for oral sedation in dentistry are midazolam, diazepam,

triazolam and lorazepam as mainstream drugs, although alprazolam, temazepam and oxazepam have also been used.[6]

Diazepam is rapidly absorbed, has a long half-life and due to its hepatic metabolism produces pharmacologically active metabolites, such as nordazepam, temazepam and oxazepam.[14] The pharmacokinetic characteristics of midazolam make it the treatment of choice. When the safety of midazolam was evaluated, it was observed that complications seem to be transient.[15] Benzodiazepines have a high therapeutic index and, therefore, a high safety margin compared with other classes of sedative hypnotics.[16]

Recent systematic reviews on sedation methods in dentistry have been published, one of which was aimed at children.[17] Despite a great variety of drugs used for conscious sedation in dentistry, there are only a few systematic reviews comparing their effectiveness and safety in adults,[10] hence the need for further targeted reviews specifically for oral sedation in adults, including evaluation criteria for quality of evidence.

OBJECTIVES

The aim of this systematic review is to determine whether benzodiazepines and other drug interventions administered orally are effective and safe in controlling anxiety in adult patients undergoing dental surgical procedures.

METHODS AND ANALYSES

This systematic review will be conducted in accordance with the recommendations specified by the Cochrane Handbook for Intervention Reviews. Evaluation will be performed following the items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement.[18]

Protocol and Registration

Our review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42017057142) (http://www.crd.york.ac.uk/PROSPERO)

Eligibility criteria

Inclusion criteria

Patients: Adult outpatients, both sexes, requiring dental surgical procedures, such as simple exodontia, surgery for orthodontic purposes, removal of residual roots and third molars, dental implants, etc.

Interventions: Studies in at least one arm should include the use of oral sedation with benzodiazepines or other drugs in adult patients and in the other arm placebo (same route of administration as the test sedative) or other treatment.

Design types: Randomised Controlled Trial (RCT).

Exclusion criteria

Studies including adults with respiratory diseases, contraindications to benzodiazepines, pregnant and/or breastfeeding women and those with a history of allergy will be excluded. In addition, studies combining administration of different drugs for oral sedation will also be excluded.

Measured outcomes

Studies should report at least one of the following outcomes: primary outcomes (pain, anxiety and adverse effects, e.g. hypoxemia and amnesia) and secondary outcomes (heart rate, respiratory rate, blood pressure and patient cooperation during the intervention).

Search methods

The search for studies will be performed using the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), which includes Dentistry & Oral Health Group's Specialized Register; MEDLINE (via Ovid);

EMBASE (via Ovid); CINAHL (via Ovid); Lilacs (Scielo); and Capes database, without restriction of language or date of issuance.

The search strategy will be conducted reviewers individually based on keywords such as oral surgery, benzodiazepines, and other drugs combined. The search strategy in Ovid Medline is available in Appendix 1.

For review articles, one of the reviewers will analyse the reference list or citation in the text in order to verify and identify other possible eligible studies. Whenever necessary, main authors and/or pharmaceutical companies involved in the production of the drugs will be contacted for information on additional trials.

Study eligibility determination

Four reviewers (JOA, CCB, CCG and NKA), working in pairs, will independently screen citations and abstracts based on the eligibility criteria. Full texts of all articles will be obtained in case either reviewer feels that they might be eligible. Two reviewers will independently assess the eligibility of each full-text article and resolve disagreements by consensus. In case of duplicate publications, the article with the most complete data will be used.

Kappa statistics will be used to measure agreement between the examiners. Values of kappa between 0.40 and 0.59 will be considered fair agreement, values between 0.60 and 0.8 good agreement and values equals to or higher than 0.75 excellent agreement.[19]

Data extraction

The reviewers will use a standardized and pre-tested form for data extraction. For articles published as abstracts only, or articles lacking important information, an attempt to obtain complete data on methods and results will be made by contacting the authors.

Two reviewers, in pairs and independently, will be calibrated based on data extraction from three articles, initially, and then, consensus will be reached. This procedure will continue until the reviewers are able to extract data in a standardized manner to minimise discrepancies.

Risk of bias of individual studies

A modified version for the Cochrane collaboration approach will be used for assessing risk of bias.[20-22] Reviewers will independently evaluate the risk of bias for each randomized study according to the following criteria: adequate randomisation, allocation concealment and blindness of patient, health professional and outcome evaluators, clearly stated outcomes and unbalance in the characterization measurements of the sample (*baseline)*. Reviewers will attribute standard answers such as “definitely yes,” “probably yes,” “probably no,” and “definitely no” for each domain, with “definitely yes” and “probably yes” denoting a low risk of bias, and “definitely no” and “probably no” attributing a high risk of bias.[23] Reviewers will resolve any disagreement by discussing them, and a third person will assess the unresolved ones.

Quality of the evidence analysis

The quality of the evidence will be independently analysed (confidence in effect estimates) for each of the results via the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[19,24] In the GRADE approach, randomised studies start with low evidence according to one or more of the five categories of limitation: risk of partiality, incoherence, indirect, inaccuracy, and bias of information.

Explaining heterogeneity of evidence

Possible complications for heterogeneity include drug types, doses (higher *vs.* lower) with greater effect than expected at higher doses and treatment time (longer vs. shorter), and doses with greater effect than expected with longer treatment time; heterogeneity will be assessed in terms of estimates of combined effect using the chi-square test and I^2 statistic.[25] Heterogeneity will be categorized as 0%–25% (low heterogeneity); 50% (moderate heterogeneity); or 75% (high heterogeneity).[22]

Data synthesis

Intervention drug, intervention group, and each outcome of interest will be analysed. Confidence in the estimates for each group will be determined and analysis for body of evidence will be performed on those with higher confidence. The hypothesis will be examined for which information will be documented on at least 10 studies for the independent variables or at least five studies for the independent categorical variables.

Combined analysis will estimate the risks of negative outcomes such as anxiety and side effects of oral sedation.

Meta-analysis will be conducted using STATA (version 10.1) for random effect,[26] which is conservative with each study, and differences in the error calculation between studies will be used for the analysis. For the studies with dichotomous outcomes, relative risk will be calculated as well as 95% confidence intervals (95% CI).

For continuous data, the weighted mean difference (WMD) and their 95%CI as effect measurement will be used. Once the WMD is calculated, this value will be contextualised, taking into account, whenever available, the minimal important difference (MID); the smallest change in the measurement will be considered important for the patient.

If studies report the same construction, using different instruments of measurement, the standardised mean difference (SMD) will be calculated as sensitivity analysis. SMD expresses the effect of the intervention in units of standard deviation, instead of initial measurement units, with the value of SMD depending on the size of the effect (the difference between the means) and the standard deviation of the results (the inherent variability amongst the participants). Measurements of results that present MID, will be used to convert SMD to an odd ratio and difference of risk.[27]

In order to facilitate interpretation of effects of continuous outcome, MID will be replaced by standard deviation (denominator) in the WMD equation[28], whenever available for different scales. If an MID estimate is not available, a statistical approach will be used to provide an estimate of a proportion of patients who would benefit from the treatment in all studies.[29] Statistical approaches to enhance interpretation of results from continuous outcomes

described herein will be included in the methods. Funnel plots will be created to explore possible biases of publication, when at least 10 studies are found.[30]

Combined estimates will be tested by Z statistics and heterogeneity by Q statistics between the studies analysed by the chi-square test. When heterogeneity is detected, a component of variance due to inter-study variability will incorporate the calculation of the confidence interval for the estimate. Studies that do not include any of the above data will not be included in the grouped estimate; for such studies, bleeding rates will be summarised descriptively.

Approaches recently developed to deal with dichotomous[31] and continuous[32] outcomes will be performed. These approaches will be applied to results that meet the following criteria: significant effect in treatment is demonstrated and data loss is sufficient to potentially introduce clinically important bias. The threshold for loss of participants data will be determined for each outcome.

If meta-analysis is not appropriate because of excessive heterogeneity of population, intervention, comparator, outcome or methodology, then summary charts will be developed and a narrative synthesis will be provided.

Summarizing evidence

Results will be presented in evidence profiles, as recommended by the work group GRADE.[33,34] Evidence profiles will provide succinct presentations of the quality of the evidence and magnitude of effects. An evidence profile will be built aided by software, GRADEpro (http://ims.cochrane.org/gradepro) in order to include the following seven elements: (1) a list of up to seven important results (desirable and undesirable); (2) a measure of typical load of such results (i.e., control, group and estimated risk); (3) a measure of the difference between the risks with and without intervention; (4) the greatness regarding effect; (5) number of participants and studies that approach these outcomes, as well as follow-up period; (6) an evaluation of the global confidence in the estimate of effect for each outcome; and (7) comments, which will include MID, whenever available. In the GRADE approach, randomised studies start with high-quality evidence, but may be evaluated as low evidence due to one or more of the five

limiting categories: risk of partiality, incoherence, speculation, inaccuracy, and information bias.

DISCUSSION

This review will evaluate the available evidence regarding the efficacy and safety of oral sedation in adult patients undergoing dental surgical interventions, such as exodontia and dental implants, in order to provide estimates of evidence in a complete and consistent manner, using the GRADE approach.[35] The results of this systematic review will help dentists in the decision-making process in clinical practice for the best oral sedation choice for patients undergoing surgical procedures.

The information compiled regarding the use of conscious sedation by oral route in patients who will require ambulatorial surgical intervention aims to provide professionals with reliable data on effectiveness and safety of pharmacological agents in such interventions; thus facilitating clinical decisions. This study may also identify areas of interest for future investigations.

Ethics and dissemination

Ethics approval is not required, as this is a protocol for a systematic review. The systematic review will be published in a peer-reviewed journal and presented at conferences. The evidence reported in this study will allow dentists to know about the effectiveness and safety of oral sedation. Updates of this study will be conducted in order to inform and guide clinical practice.

Abbreviations

Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Virtual Health Library (VHL), Grading of Recommendations Assessment, Development, and Evaluation (GRADE), Randomized clinical trial (RCT), 95% confidence interval (95% CI), Weighted Mean Difference (WMD), Minimal Important Difference (MID).

Contributor ship statement

JOA is the principal investigator and led the writing of the manuscript. LCL and RHLM are the project managers, co-investigators and contributed to the writing and revision of the manuscript. CCB, NKA, CCG, JCR and MFF are co-investigators and contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Appendix 1 - Search strategy (Via Ovid)

1. surgery, maxillofacial.mp. or exp Surgery, Oral/
2. operative dentistry.mp. or exp Dentistry, Operative/
3. dentistry, operative.mp. or exp Dentistry, Operative/
4. prosthesis, surgical dental.mp. or Dental Implants/
5. prostheses, surgical dental.mp. or exp Dental Implants/
6. surgical dental prosthesis.mp. or exp Dental Implants/
7. surgical dental prostheses.mp. or exp Dental Implants/
8. dental prosthesis, surgical.mp. or exp Dental Implants/
9. dental prostheses, surgical.mp. or exp Dental Implants/
10. implant, dental.mp. or exp Dental Implants/
11. dental implant.mp. or exp Dental Implants/
12. implants, dental.mp. or exp Dental Implants/
13. dental implants.mp. or exp Dental Implants/
14. procedures, maxillofacial.mp. or exp Oral Surgical Procedures/
15. procedure, maxillofacial.mp. or exp Oral Surgical Procedures/
16. maxillofacial procedure.mp. or exp Oral Surgical Procedures/
17. maxillofacial procedures.mp. or exp Oral Surgical Procedures/
18. exodontics.mp. or exp Surgery, Oral/
19. procedure, oral surgical.mp. or exp Oral Surgical Procedures/
20. oral surgical procedure.mp. or exp Oral Surgical Procedures/
21. surgical procedures, oral.mp. or exp Oral Surgical Procedures/
22. procedures, oral surgical.mp. or exp Oral Surgical Procedures/
23. surgical procedures, oral.mp. or exp Oral Surgical Procedures/
24. oral surgical procedures.mp. or exp Oral Surgical Procedures/
25. oral surgery.mp. or exp Surgery, Oral/
26. maxillofacial surgery.mp. or exp Surgery, Oral/
27. surgery,oral.mp. or exp Surgery, Oral/

28. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. benzodiazepinones.mp. or exp Benzodiazepinones/
30. Benzodiazepinones.mp. or exp Benzodiazepinones/
31. Alprazolam novopharm brand.mp. or exp Alprazolam/
32. novopharm brand of alprazolam.mp. or exp Alprazolam/
33. novo alprazol.mp. or exp Alprazolam/
34. novoalprazol.mp. or exp Alprazolam/
35. novo-alprazol.mp. or exp Alprazolam/
36. Alprazolam pfizer brand.mp. or exp Alprazolam/
37. pfizer brand of alprazolam.mp. or exp Alprazolam/
38. maleate, midazolam.mp. or exp Midazolam/
39. midazolam maleate.mp. or exp Midazolam/
40. midazolam.mp. or exp Midazolam/
41. effect, antianxiety.mp. or exp Anti-Anxiety Agents/
42. antianxiety effect.mp. or exp Anti-Anxiety Agents/
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45. anti-anxiety effects.mp. or exp Anti-Anxiety Agents/
46. effect, anxiolytic.mp. or exp Anti-Anxiety Agents/
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51. anxiolytic effects.mp. or exp Anti-Anxiety Agents/
52. effect,anti-anxiety.mp. or exp Anti-Anxiety Agents/
53. anti anxiety effect.mp. or exp Anti-Anxiety Agents/
54. anti-anxiety effect.mp. or exp Anti-Anxiety Agents/
55. anxiolytics.mp. or exp Anti-Anxiety Agents/
56. drugs, anti-anxiety.mp. or exp Anti-Anxiety Agents/
57. anti anxiety drugs.mp. or exp Anti-Anxiety Agents/

58. anti-anxiety drugs.mp. or exp Anti-Anxiety Agents/
59. minor tranquillizing agents.mp. or exp Anti-Anxiety Agents/
60. agents, minor tranquillizing.mp. or exp Anti-Anxiety Agents/
61. minor tranquilizing agents.mp. or exp Anti-Anxiety Agents/
62. agents, minor tranquilizing.mp. or exp Anti-Anxiety Agents/
63. tranquilizing agents, minor.mp. or exp Anti-Anxiety Agents/
64. agents, anxiolytic.mp. or exp Anti-Anxiety Agents/
65. anxiolytic agents.mp. or exp Anti-Anxiety Agents/
66. anti anxiety agents.mp. or exp Anti-Anxiety Agents/
67. agents, anti-anxiety.mp. or exp Anti-Anxiety Agents/
68. anti-anxiety agents.mp. or exp Anti-Anxiety Agents/
69. **29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68**

70. 69 and 28

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review – **PAGE 1**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **NOT APPLICABLE**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number - **PAGE 5**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author – **PAGE 1**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review – **PAGE 11**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments **NOT APPLICABLE**
Support:		
Sources	5a	Indicate sources of financial or other support for the review – **PAGE 11**
Sponsor	5b	Provide name for the review funder and/or sponsor - **NOT APPLICABLE**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **NOT APPLICABLE**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known – **PAGES 3, 4**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) – **PAGE 4**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review – **PAGE 5**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage – **PAGE 6**
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated - **PAGE 6**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **PAGE 6**

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) **PAGES 6, 7**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators **PAGES 7, 8**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications **PAGES 8-10**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **PAGE 5**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis **PAGE 7**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **PAGES 8, 9**
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) **PAGES 8, 9**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **PAGE 10**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **PAGE 9**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting **PAGES 9, 10**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **PAGES 9, 10**

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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BMJ Open

Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: protocol for a systematic review

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Primary Subject Heading:	Dentistry and oral medicine
Secondary Subject Heading:	Dentistry and oral medicine
Keywords:	Conscious Sedation, Oral Surgery, Dentistry, Dental anxiety, Benzodiazepines, Administration, Oral

Title: Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: protocol for a systematic review

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ABSTRACT

Introduction: The management of anxious patients undergoing dental procedures is still a challenge in clinical practice. Despite a wide variety of drugs for oral sedation in adult patients, there are relatively few systematic reviews that compare the effectiveness and safety of different drugs administered via this route. This study will evaluate the effectiveness and safety of oral sedation with benzodiazepines and other agents to patients undergoing dental surgical procedures.

Method/Design: We will conduct a systematic review and, if appropriate, a meta-analysis of randomised controlled clinical trials that will evaluate the use of sedation administered orally to adult patients undergoing oral surgery. The search will be conducted using electronic databases, such as the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via Ovid); EMBASE (via Ovid); CINAHL (via Ovid); Lilacs (Scielo); and Capes database, without restriction of languages or date of publication. Primary outcomes include anxiety, sedation, treatment satisfaction, pain and adverse effects. Secondary outcomes include vital parameters (heart rate, respiratory rate and blood pressure) and patient cooperation during intervention. A team of reviewers will independently assess each citation for eligibility and in duplicates. For eligible studies, the same reviewers will perform data extraction, risk of bias assessment and determination of the overall quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) classification system.

Ethics and Dissemination: The evidence gathered from this study should provide dental surgeons with knowledge on the effectiveness and safety of oral sedation in adults requiring dental surgical procedures. This in turn should contribute towards the decision-making process in dental practice, minimizing the risks of anxiety and ineffective pain control in clinical procedures, as well as possible side effects. Ethics approval is not required in protocols for systematic reviews. The systematic review will be published in a peer-reviewed journal and presented at conferences.

Protocol registration: PROSPERO - CRD42017057142

Strengths and limitations of this study

- Anxiety and risk of adverse effects with the use of sedatives are negative outcomes in dentistry that may interfere with preoperative, intraoperative and postoperative effects relating to surgical interventions in dental practice. Estimating the risk rate of such events in patients treated with oral sedation may contribute to the decision-making process regarding conscious sedation.
- This study will provide a summary on safety for the commonly used oral sedative drugs for conscious sedation in dentistry.
- The quality of the primary studies to be included in this review may be a limiting factor due to heterogeneity in study design and outcome measurements.

INTRODUCTION

Effective control of anxiety and pain plays a pivotal role on patient compliance and adherence to dental treatment. For behavioural management, the use of analgesia and conscious sedation are important strategies for treating patients who suffer from anxiety to dental treatment.[1]

Conscious sedation is an approach that uses one or more drugs to produce a state of central nervous system depression maintaining verbal contact with the patient throughout.[2] The sedation level must be such that the patient remains conscious and is capable of readily understanding and answering verbal commands or tactile stimulation.[3] Drug interventions to provide conscious sedation for dental treatment must have a wide enough safety margin so that loss of consciousness is unlikely to happen.[4] In addition, considering the different methods of sedation and patient profiles in dental care, monitoring procedures and documentation have been recommended.[3,5,6]

Among the different types of sedation in dentistry, oral sedation is a relatively acessible means for dentists to address patient anxiety when chairside manner alone is insufficient.[6] Moreover, it involves the administration of a relatively large dose of oral sedatives in dental practice, which differs from the concept of pre medication, which involves self-administration of a small dose of oral sedative to relieve anxiety.[3] As any other approach, oral sedation

may present some limitations due to the pharmacokinetics relating to the oral route, such as delayed and variable onset of action.[6] Although it may help patients with mild to moderate levels of anxiety, this technique may be not effective in severely anxious patients.[7]

Oral sedation does not guarantee that a dental patient will achieve a state of anxiolysis or will not drift into deeper levels of sedation.[7] Since sedation is a continuum, it is not always possible to predict how an individual will respond. Therefore, practitioners intending to obtain a given level of sedation should also be able to rescue patients should they become overly sedated.[8] Indications for the use of conscious sedation as a patient management tool include a diagnosis of anxiety and dental phobia, prolonged or traumatic dental procedures, medical conditions potentially aggravated by stress, and medical conditions that affect the capacity of the patient to cooperate, such as special needs.[9]

Benzodiazepines are the class of drugs most often used in dentistry to induce a state of anxiolysis[10] and are the drugs of choice for oral sedation in several countries,[3,6,7,11] although sublingual and intravenous administration are also available.[12,13] Historically, temazepam has been the drug of choice for oral sedation in dentistry in some countries, but its use has been largely replaced by midazolam.[3]

Although these drugs have a similar mechanism of action, they differ on pharmacokinetic characteristics, which in turn play an important role on selecting the best option to suit an patient's profile.[5] Among the different options for oral sedation in dentistry are midazolam, diazepam, triazolam and lorazepam as mainstream drugs, although alprazolam, temazepam and oxazepam have also been used.[6]

Despite a great variety of drugs used for conscious sedation in dentistry, there are only a few systematic reviews comparing their effectiveness and safety for oral sedation in adults. One systematic review evaluated the use of these drugs in adults but did not assess the risk of bias and the quality of the evidence of the outcomes found.[10] Another systematic review study on sedation methods in dentistry verified the effectiveness of benzodiazepines at children.[14] Hence, to fill this gap, we propose a systematic review to determine whether

benzodiazepines and other drug interventions administered orally are effective and safe in controlling anxiety in adult patients undergoing dental surgical procedures.

METHODS AND ANALYSES

This systematic review will be conducted in accordance with the recommendations specified by the Cochrane Handbook for Intervention Reviews. Evaluation will be performed following the items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement.[15]

Protocol and Registration

Our review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42017057142) (http://www.crd.york.ac.uk/PROSPERO)

Eligibility criteria

Inclusion criteria

Patients: Adult outpatients, both sexes, requiring dental surgical procedures, such as simple exodontia, surgery for orthodontic purposes, removal of residual roots and third molars, dental implants, and other dental surgical interventions.

Interventions: Studies in at least one arm should include the use of oral sedation with benzodiazepines or other drugs in adult patients and in the other arm placebo (same route of administration as the test sedative) or other treatment.

Design types: Randomised Controlled Trial (RCT).

Exclusion criteria

Studies including adults with respiratory diseases, contraindications to benzodiazepines, pregnant and/or breastfeeding women and those with a history of allergy will be excluded. In addition, studies combining administration of different drugs for oral sedation will also be excluded.

Measured outcomes

Studies should report at least one of the following outcomes: primary outcomes (pain, anxiety and adverse effects, e.g. hypoxemia and amnesia) and secondary outcomes (heart rate, respiratory rate, blood pressure and patient cooperation during the intervention).

Search methods

The search for studies will be performed using the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), which includes Dentistry & Oral Health Group's Specialized Register; MEDLINE (via Ovid); EMBASE (via Ovid); CINAHL (via Ovid); Lilacs (Scielo); and Capes database, without restriction of languages or date of publication.

The search strategy will be conducted reviewers individually based on keywords such as oral surgery, benzodiazepines, and other drugs combined. The search strategy in Ovid Medline is available in Appendix 1.

For review articles, one of the reviewers will analyse the reference list or citation in the text in order to verify and identify other possible eligible studies. Whenever necessary, main authors and/or pharmaceutical companies involved in the production of the drugs will be contacted for information on additional trials.

Study eligibility determination

Four reviewers (JOA, CCB, CCG and NKA), working in pairs, will independently screen citations and abstracts based on the eligibility criteria. Full texts of all articles will be obtained in case either reviewer feels that they might be eligible. Two reviewers will independently assess the eligibility of each full-text article and resolve disagreements by consensus. In case of duplicate publications, the article with the most complete data will be used.

Kappa statistics will be used to measure agreement between the examiners. Values of kappa between 0.40 and 0.59 will be considered fair agreement, values between 0.60 and 0.80 good agreement and values equals to or higher than 0.75 excellent agreement.[16]

Data extraction

The reviewers will use a standardised and pre-tested form for data extraction. For articles published as abstracts only, or articles lacking important information, an attempt to obtain complete data on methods and results will be made by contacting the authors.

Two reviewers, in pairs and independently, will be calibrated based on data extraction from three articles, initially, and then, consensus will be reached. This procedure will continue until the reviewers are able to extract data in a standardised manner to minimise discrepancies.

Risk of bias of individual studies

A modified version for the Cochrane collaboration approach will be used for assessing risk of bias.[17-19] Reviewers will independently evaluate the risk of bias for each randomised study according to the following criteria: adequate randomisation, allocation concealment blinding of the patient, healthcare professionals, outcome assessors, data collectors and data analysts; incomplete outcome data; selective outcome reporting; and major baseline imbalance. Reviewers will attribute standard answers such as “definitely yes,” “probably yes,” “probably no,” and “definitely no” for each domain, with “definitely yes” and “probably yes” denoting a low risk of bias, and “definitely no” and “probably no” attributing a high risk of bias.[20] Reviewers will resolve disagreements debating, and one arbitrator (LCL) will settle unresolved disagreements.

Quality of the evidence analysis

The quality of the evidence will be independently analysed (confidence in effect estimates) for each of the results via the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[16,21] In the GRADE approach, randomised studies start with low evidence according to one or more of the five categories of limitation: risk of bias, inconsistency, indirectness, imprecision, and reporting bias.

Explaining heterogeneity of evidence

Possible complications for heterogeneity include drug types, doses (higher *vs.* lower) with greater effect than expected at higher doses and treatment time (longer vs. shorter), and doses with greater effect than expected with longer treatment time; heterogeneity will be assessed in terms of estimates of combined effect using the chi-square test and I^2 statistic.[22] Heterogeneity will be categorised as until 25% (low heterogeneity); 50% (moderate heterogeneity); or 75% (high heterogeneity).[19]

Data synthesis

Intervention drug, intervention group, and each outcome of interest will be analysed. Confidence in the estimates for each group will be determined and analysis for body of evidence will be performed on those with higher confidence. The hypothesis will be examined for which information will be documented on at least 10 studies for the independent variables or at least five studies for the independent categorical variables. Combined analysis will estimate the risks of negative outcomes such as anxiety and side effects of oral sedation.

Meta-analysis will be conducted using STATA (version 10.1) for random effect,[23] which is conservative with each study, and differences in the error calculation between studies will be used for the analysis. For the studies with dichotomous outcomes, relative risk will be calculated as well as 95% confidence intervals (95% CI).

For continuous data, the weighted mean difference (WMD) and their 95%CI as effect measurement will be used. Once the WMD is calculated, this value will be contextualised, taking into account, whenever available, the minimal important difference (MID); the smallest change in the measurement will be considered important for the patient.

If studies report the same construction, using different instruments of measurement, the standardised mean difference (SMD) will be calculated as sensitivity analysis. SMD expresses the effect of the intervention in units of standard deviation, instead of initial measurement units, with the value of SMD depending on the size of the effect (the difference between the means) and the standard deviation of the results (the inherent variability amongst the

participants). Measurements of results that present MID, will be used to convert SMD to an odd ratio and difference of risk.[24]

In order to facilitate interpretation of effects of continuous outcome, MID will be replaced by standard deviation (denominator) in the WMD equation[25], whenever available for different scales. If an MID estimate is not available, a statistical approach will be used to provide an estimate of a proportion of patients who would benefit from the treatment in all studies.[26] Statistical approaches to enhance interpretation of results from continuous outcomes described herein will be included in the methods. Funnel plots will be created to explore possible biases of publication, when at least 10 studies are found.[27]

Combined estimates will be tested by Z statistics and heterogeneity by Q statistics between the studies analysed by the chi-square test. When heterogeneity is detected, a component of variance due to inter-study variability will incorporate the calculation of the confidence interval for the estimate. Studies that do not include any of the above data will not be included in the grouped estimate; for such studies, bleeding rates will be summarised descriptively.

Approaches recently developed to deal with dichotomous[28] and continuous[29] outcomes will be performed. These approaches will be applied to results that meet the following criteria: significant effect in treatment is demonstrated and data loss is sufficient to potentially introduce clinically important bias. The threshold for loss of participant's data will be determined for each outcome.

If meta-analysis is not appropriate because of excessive heterogeneity of population, intervention, comparator, outcome or methodology, then summary charts will be developed and a narrative synthesis will be provided.

Summarizing evidence

Results will be presented in evidence profiles, as recommended by the work group GRADE.[30,31] Evidence profiles will provide succinct presentations of the quality of the evidence and magnitude of effects. An evidence profile will be built aided by software, GRADEpro (http://ims.cochrane.org/gradepro) in order to include the following seven elements: (1) a list of up to seven important results (desirable and undesirable); (2) a measure of typical load of such results

(i.e., control, group and estimated risk); (3) a measure of the difference between the risks with and without intervention; (4) the greatness regarding effect; (5) number of participants and studies that approach these outcomes, as well as follow-up period; (6) an evaluation of the global confidence in the estimate of effect for each outcome; and (7) comments, which will include MID, whenever available. In the GRADE approach, randomised trials begin as high-quality evidence but may be rated down by one or more of five categories of limitations: risk of bias, inconsistency, indirectness, imprecision, and reporting bias.

DISCUSSION

This review will evaluate the available evidence regarding the efficacy and safety of oral sedation in adult patients undergoing dental surgical interventions, such as exodontia, dental implants, surgery for orthodontic purposes and removal of residual roots and third molars in order to provide estimates of evidence in a complete and consistent manner, using the GRADE approach.[32] The results of this systematic review will help dentists in the decision-making process in clinical practice for the best oral sedation choice for patients undergoing surgical procedures.

The information compiled regarding the use of conscious sedation by oral route in patients who will require ambulatory surgical intervention aims to provide professionals with reliable data on effectiveness and safety of pharmacological agents in such interventions; thus facilitating clinical decisions. This study may also identify areas of interest for future investigations.

Ethics and dissemination

Ethics approval is not required, as this is a protocol for a systematic review. The systematic review will be published in a peer-reviewed journal and presented at conferences. The evidence reported in this study will allow dentists to know about the effectiveness and safety of oral sedation. Updates of this study will be conducted in order to inform and guide clinical practice.

Abbreviations

Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Virtual Health Library

(VHL), Grading of Recommendations Assessment, Development, and Evaluation (GRADE), Randomised Clinical Trial (RCT), 95% Confidence Interval (95% CI), Weighted Mean Difference (WMD), Minimal Important Difference (MID).

Contributor ship statement

JOA is the principal investigator and led the writing of the manuscript. LCL and RHLM are the project managers, co-investigators and contributed to the writing and revision of the manuscript. CCB, NKA, CCG, JCR and MFF are co-investigators and contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Appendix 1 - Search strategy (Via Ovid)

1. surgery, maxillofacial.mp. or exp Surgery, Oral/
2. operative dentistry.mp. or exp Dentistry, Operative/
3. dentistry, operative.mp. or exp Dentistry, Operative/
4. prosthesis, surgical dental.mp. or Dental Implants/
5. prostheses, surgical dental.mp. or exp Dental Implants/
6. surgical dental prosthesis.mp. or exp Dental Implants/
7. surgical dental prostheses.mp. or exp Dental Implants/
8. dental prosthesis, surgical.mp. or exp Dental Implants/
9. dental prostheses, surgical.mp. or exp Dental Implants/
10. implant, dental.mp. or exp Dental Implants/
11. dental implant.mp. or exp Dental Implants/
12. implants, dental.mp. or exp Dental Implants/
13. dental implants.mp. or exp Dental Implants/
14. procedures, maxillofacial.mp. or exp Oral Surgical Procedures/
15. procedure, maxillofacial.mp. or exp Oral Surgical Procedures/
16. maxillofacial procedure.mp. or exp Oral Surgical Procedures/
17. maxillofacial procedures.mp. or exp Oral Surgical Procedures/
18. exodontics.mp. or exp Surgery, Oral/
19. procedure, oral surgical.mp. or exp Oral Surgical Procedures/
20. oral surgical procedure.mp. or exp Oral Surgical Procedures/
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27. surgery,oral.mp. or exp Surgery, Oral/

28. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. benzodiazepinones.mp. or exp Benzodiazepinones/
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31. Alprazolam novopharm brand.mp. or exp Alprazolam/
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review – **PAGE 1**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **NOT APPLICABLE**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number - **PAGE 5**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author – **PAGE 1**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review – **PAGE 11**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments **NOT APPLICABLE**
Support:		
Sources	5a	Indicate sources of financial or other support for the review – **PAGE 11**
Sponsor	5b	Provide name for the review funder and/or sponsor - **NOT APPLICABLE**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **NOT APPLICABLE**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known – **PAGES 3, 4**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) – **PAGE 4**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review – **PAGE 5**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage – **PAGE 6**
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated - **PAGE 6**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **PAGE 6**

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) **PAGES 6, 7**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators **PAGES 7, 8**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications **PAGES 8-10**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **PAGE 5**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis **PAGE 7**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **PAGES 8, 9**
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) **PAGES 8, 9**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **PAGE 10**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **PAGE 9**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting **PAGES 9, 10**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **PAGES 9, 10**

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: protocol for a systematic review

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Title: Effectiveness and safety of oral sedation in adult patients undergoing dental procedures: protocol for a systematic review

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ABSTRACT

Introduction: The management of anxious patients undergoing dental procedures is still a challenge in clinical practice. Despite a wide variety of drugs for oral sedation in adult patients, there are relatively few systematic reviews that compare the effectiveness and safety of different drugs administered via this route. Thus, this study will evaluate the effectiveness and safety of oral sedation with benzodiazepines and other agents to patients undergoing dental surgical procedures.

Method/Design: We will conduct a systematic review and, if appropriate, a meta-analysis of randomised controlled clinical trials that will evaluate the use of conscious sedation administered orally to adult patients undergoing oral surgery. The search will be conducted using electronic databases, such as the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via Ovid); EMBASE (via Ovid); CINAHL (via Ovid); Lilacs (Scielo); and Capes database, without restriction of languages or date of publication. Primary outcomes include anxiety, sedation, treatment satisfaction, pain and adverse effects. Secondary outcomes include vital parameters (heart rate, respiratory rate and blood pressure) and patient cooperation during intervention. A team of reviewers will independently assess each citation for eligibility and in duplicates. For eligible studies, the same reviewers will perform data extraction, risk of bias assessment and determination of the overall quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) classification system.

Ethics and Dissemination: The evidence gathered from this study should provide dental surgeons with knowledge on the effectiveness and safety of oral sedation in adults requiring dental surgical procedures. This in turn should contribute towards the decision-making process in dental practice, minimizing the risks of anxiety and ineffective pain control in clinical procedures, as well as possible side effects. Ethics approval is not required in protocols for systematic reviews. The systematic review will be published in a peer-reviewed journal and presented at conferences.

Protocol registration: PROSPERO - CRD42017057142

Strengths and limitations of this study

- Anxiety and risk of adverse effects with the use of sedatives are negative outcomes in dentistry that may interfere with preoperative, intraoperative and postoperative effects relating to surgical interventions in dental practice. Estimating the risk rate of such events in patients treated with oral sedation may contribute to the decision-making process regarding conscious sedation.
- This study will provide a summary on safety for the commonly used oral sedative drugs for conscious sedation in dentistry.
- The quality of the primary studies to be included in this review may be a limiting factor due to heterogeneity in study design and outcome measurements.

INTRODUCTION

Effective control of anxiety and pain plays a pivotal role on patient compliance and adherence to dental treatment. For behavioural management, the use of analgesia and conscious sedation are important strategies for treating patients who suffer from anxiety to dental treatment.[1]

Conscious sedation is an approach that uses one or more drugs to produce a state of central nervous system depression maintaining verbal contact with the patient throughout.[2] The sedation level must be such that the patient remains conscious and is capable of readily understanding and answering verbal commands or tactile stimulation.[3] Drug interventions to provide conscious sedation for dental treatment must have a wide enough safety margin so that loss of consciousness is unlikely to happen.[4] In addition, considering the different methods of sedation and patient profiles in dental care, monitoring procedures and documentation have been recommended.[3,5,6]

Among the different types of sedation in dentistry, oral sedation is a relatively acessible means for dentists to address patient anxiety when chairside manner alone is insufficient.[6] Moreover, it involves the administration of a relatively large dose of oral sedatives in dental practice, which differs from the concept of pre medication, which involves self-administration of a small dose of oral sedative to relieve anxiety.[3] As any other approach, oral sedation

may present some limitations due to the pharmacokinetics relating to the oral route, such as delayed and variable onset of action.[6] Although it may help patients with mild to moderate levels of anxiety, this technique may be not effective in severely anxious patients.[7]

Oral sedation does not guarantee that a dental patient will achieve a state of anxiolysis or will not drift into deeper levels of sedation.[7] Since sedation is a continuum, it is not always possible to predict how an individual will respond. Therefore, practitioners intending to obtain a given level of sedation should also be able to rescue patients should they become overly sedated.[8] Indications for the use of conscious sedation as a patient management tool include a diagnosis of anxiety and dental phobia, prolonged or traumatic dental procedures, medical conditions potentially aggravated by stress, and medical conditions that affect the capacity of the patient to cooperate, such as special needs.[9]

Benzodiazepines are the class of drugs most often used in dentistry to induce a state of anxiolysis[10] and are the drugs of choice for oral sedation in several countries,[3,6,7,11] although sublingual and intravenous administration are also available.[12,13] Historically, temazepam has been the drug of choice for oral sedation in dentistry in some countries, but its use has been largely replaced by midazolam.[3]

Although these drugs have a similar mechanism of action, they differ on pharmacokinetic characteristics, which in turn play an important role on selecting the best option to suit an patient's profile.[5] Among the different options for oral sedation in dentistry are midazolam, diazepam, triazolam and lorazepam as mainstream drugs, although alprazolam, temazepam and oxazepam have also been used.[6]

Despite a great variety of drugs used for conscious sedation in dentistry, there are only a few systematic reviews comparing their effectiveness and safety for oral sedation in adults. One systematic review evaluated the use of these drugs in adults but did not assess the risk of bias and the quality of the evidence of the outcomes found.[10] Another systematic review study on sedation methods in dentistry verified the effectiveness of benzodiazepines at children.[14] Hence, to fill this gap, we propose a systematic review to determine whether

benzodiazepines and other drug interventions administered orally are effective and safe in controlling anxiety in adult patients undergoing dental surgical procedures.

METHODS AND ANALYSES

This systematic review will be conducted in accordance with the recommendations specified by the Cochrane Handbook for Intervention Reviews. Evaluation will be performed following the items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement.[15]

Protocol and Registration

Our review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42017057142) (http://www.crd.york.ac.uk/PROSPERO)

Eligibility criteria

The studies will be selected according to the following criteria:

Study designs

We will include only Randomised Controlled Trial (RCT) in that at least one arm should include the use of oral sedation with benzodiazepines or other drugs in adult patients, and in the other arm placebo (same route of administration as the test sedative) or other treatment.

Participants

We will include studies that report adult outpatients, both sexes, requiring dental surgical procedures, such as simple exodontia, surgery for orthodontic purposes, removal of residual roots and third molars, dental implants, and other dental surgical interventions.

Exclusion criteria

We will include studies including adults with respiratory diseases, contraindications to benzodiazepines, pregnant and/or breastfeeding women and those with a history of allergy will be excluded. In addition, studies combining administration of different drugs for oral sedation will also be excluded.

Outcomes

Studies should report at least one of the following outcomes: primary outcomes (pain, anxiety and adverse effects, e.g. hypoxemia and amnesia) and secondary outcomes (heart rate, respiratory rate, blood pressure and patient cooperation during the intervention).

Information sources

The search for studies will be performed using the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), which includes Dentistry & Oral Health Group's Specialized Register; MEDLINE (via Ovid); EMBASE (via Ovid); CINAHL (via Ovid); Lilacs (Scielo); and Capes database, without restriction of languages or date of publication.

For review articles, one of the reviewers will analyse the reference list or citation in the text in order to verify and identify other possible eligible studies. Whenever necessary, main authors and/or pharmaceutical companies involved in the production of the drugs will be contacted for information on additional trials.

Search strategies

The search strategy will be conducted reviewers individually based on keywords such as oral surgery, benzodiazepines, and other drugs combined. The search strategy in Ovid Medline is available in Appendix 1.

Study records

Data management

After performing the search strategies separately in each electronic database, the researchers will import the results from each search into an

EndNote library. As the same article may be located in more than one database, duplicate entries will be identified and removed.

Study eligibility determination

Four reviewers (JOA, CCB, CCG and NKA), working in pairs, will independently screen citations and abstracts based on the eligibility criteria. Full texts of all articles will be obtained in case either reviewer feels that they might be eligible. Two reviewers will independently assess the eligibility of each full-text article and resolve disagreements by consensus **among the review team**. In case of duplicate publications, the article with the most complete data will be used.

Kappa statistics will be used to measure agreement between the examiners. Values of kappa between 0.40 and 0.59 will be considered fair agreement, values between 0.60 and 0.80 good agreement and values equals to or higher than 0.75 excellent agreement.[16]

Data collection

Relevant data, from eligible studies, will be independently extracted by four reviewers in excel program, using a standardised data extraction form. Extracted data will be summarised in tables and graphics. The discrepancies will be resolved by discussion and consensus among the review team.

Data items

The extracted data from each included study will include:

i. ***article details:*** year and journal of publication;

ii. study details: setting, number of participants in each group, source population, lost to follow-up and/or reasons for nonparticipation (if applicable), type of benzodiazepines, type of dental procedure and participant characteristics (age, gender and clinical condition);

iii. methodological details: measured outcomes, measure of risk of bias and measure of the body of evidence;

iv. quantitative measures: data mean/standard deviation or median/interquartile range for the outcomes evaluated;

v. other details: source of funding statement (present or absent), actual source of funding (present or absent) and conflict of interest statement (present or absent), conflict of interest type (employee of company conducting study and others).

Data extraction

The reviewers will use a standardised and pre-tested form for data extraction. For articles published as abstracts only, or articles lacking important information, an attempt to obtain complete data on methods and results will be made by contacting the authors.

Two reviewers, in pairs and independently, will be calibrated based on data extraction from three articles, initially, and then, consensus will be reached. This procedure will continue until the reviewers are able to extract data in a standardised manner to minimise discrepancies.

Assessment of risk of bias in included studies

A modified version for the Cochrane collaboration approach will be used for assessing risk of bias.[17-19] Reviewers will independently evaluate the risk of bias for each randomised study according to the following criteria: adequate randomisation, allocation concealment blinding of the patient, healthcare professionals, outcome assessors, data collectors and data analysts; incomplete outcome data; selective outcome reporting; and major baseline imbalance. Reviewers will attribute standard answers such as “definitely yes,” “probably yes,” “probably no,” and “definitely no” for each domain, with “definitely yes” and “probably yes” denoting a low risk of bias, and “definitely no” and “probably no” attributing a high risk of bias.[20] Reviewers will resolve disagreements by consensus, and one arbitrator (LCL) will settle unresolved disagreements.

Explaining heterogeneity of evidence

Possible complications for heterogeneity include drug types, doses (higher *vs.* lower) with greater effect than expected at higher doses and treatment time (longer vs. shorter), and doses with greater effect than expected with longer treatment time; heterogeneity will be assessed in terms of estimates

of combined effect using the chi-square test and I^2 statistic.[21] Heterogeneity will be categorised as until 25% (low heterogeneity); 50% (moderate heterogeneity); or 75% (high heterogeneity).[19]

Quality of the evidence analysis

The quality and strength of the body of evidence will be independently analysed (confidence in effect estimates) for each of the results via the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[16,22] In the GRADE approach, randomised studies start with low evidence according to one or more of the five categories of limitation: risk of bias, inconsistency, indirectness, imprecision, and reporting bias.

Data synthesis

Intervention drug, intervention group, and each outcome of interest will be analysed. Confidence in the estimates for each group will be determined and analysis for body of evidence will be performed on those with higher confidence. The hypothesis will be examined for which information will be documented on at least 10 studies for the independent variables or at least five studies for the independent categorical variables. Combined analysis will estimate the risks of negative outcomes such as anxiety and side effects of oral sedation.

Meta-analysis will be conducted using STATA (version 10.1) for random effect,[23] which is conservative with each study, and differences in the error calculation between studies will be used for the analysis. For the studies with dichotomous outcomes, relative risk will be calculated as well as 95% confidence intervals (95% CI).

For continuous data, the weighted mean difference (WMD) and their 95%CI as effect measurement will be used. Once the WMD is calculated, this value will be contextualised, taking into account, whenever available, the minimal important difference (MID); the smallest change in the measurement will be considered important for the patient.

If studies report the same construction, using different instruments of measurement, the standardised mean difference (SMD) will be calculated as sensitivity analysis. SMD expresses the effect of the intervention in units of standard deviation, instead of initial measurement units, with the value of SMD

depending on the size of the effect (the difference between the means) and the standard deviation of the results (the inherent variability amongst the participants). Measurements of results that present MID, will be used to convert SMD to an odd ratio and difference of risk.[24]

In order to facilitate interpretation of effects of continuous outcome, MID will be replaced by standard deviation (denominator) in the WMD equation[25], whenever available for different scales. If an MID estimate is not available, a statistical approach will be used to provide an estimate of a proportion of patients who would benefit from the treatment in all studies.[26] Statistical approaches to enhance interpretation of results from continuous outcomes described herein will be included in the methods. Funnel plots will be created to explore possible biases of publication, when at least 10 studies are found.[27]

Combined estimates will be tested by Z statistics and heterogeneity by Q statistics between the studies analysed by the chi-square test. When heterogeneity is detected, a component of variance due to inter-study variability will incorporate the calculation of the confidence interval for the estimate. Studies that do not include any of the above data will not be included in the grouped estimate; for such studies, bleeding rates will be summarised descriptively.

Approaches recently developed to deal with dichotomous[28] and continuous[29] outcomes will be performed. These approaches will be applied to results that meet the following criteria: significant effect in treatment is demonstrated and data loss is sufficient to potentially introduce clinically important bias. The threshold for loss of participant's data will be determined for each outcome.

If meta-analysis is not appropriate because of excessive heterogeneity of population, intervention, comparator, outcome or methodology, then summary charts will be developed and a narrative synthesis will be provided.

Summarizing evidence

Results will be presented in evidence profiles, as recommended by the work group GRADE.[30,31] Evidence profiles will provide succinct presentations of the quality of the evidence and magnitude of effects. An evidence profile will be built aided by software, GRADEpro (http://ims.cochrane.org/gradepro) in order

to include the following seven elements: (1) a list of up to seven important results (desirable and undesirable); (2) a measure of typical load of such results (i.e., control, group and estimated risk); (3) a measure of the difference between the risks with and without intervention; (4) the greatness regarding effect; (5) number of participants and studies that approach these outcomes, as well as follow-up period; (6) an evaluation of the global confidence in the estimate of effect for each outcome; and (7) comments, which will include MID, whenever available. In the GRADE approach, randomised trials begin as high-quality evidence but may be rated down by one or more of five categories of limitations: risk of bias, inconsistency, indirectness, imprecision, and reporting bias.

DISCUSSION

This review will evaluate the available evidence regarding the efficacy and safety of oral sedation in adult patients undergoing dental surgical interventions, such as exodontia, dental implants, surgery for orthodontic purposes and removal of residual roots and third molars in order to provide estimates of evidence in a complete and consistent manner, using the GRADE approach.[32] The results of this systematic review will help dentists in the decision-making process in clinical practice for the best oral sedation choice for patients undergoing surgical procedures.

The information compiled regarding the use of conscious sedation by oral route in patients who will require ambulatory surgical intervention aims to provide professionals with reliable data on effectiveness and safety of pharmacological agents in such interventions; thus facilitating clinical decisions. This study may also identify areas of interest for future investigations.

Ethics and dissemination

Ethics approval is not required, as this is a protocol for a systematic review. The systematic review will be published in a peer-reviewed journal and presented at conferences. The evidence reported in this study will allow dentists to know about the effectiveness and safety of oral sedation. Updates of this study will be conducted in order to inform and guide clinical practice.

Abbreviations

Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Virtual Health Library (VHL), Grading of Recommendations Assessment, Development, and Evaluation (GRADE), Randomised Clinical Trial (RCT), 95% Confidence Interval (95% CI), Weighted Mean Difference (WMD), Minimal Important Difference (MID).

Contributorship statement

JOA is the principal investigator and led the writing of the manuscript. LCL and RHLM are the project managers, co-investigators and contributed to the writing and revision of the manuscript. CCB, NKA, CCG, JCR and MFF are co-investigators and contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Appendix 1 - Search strategy (Via Ovid)

1. surgery, maxillofacial.mp. or exp Surgery, Oral/
2. operative dentistry.mp. or exp Dentistry, Operative/
3. dentistry, operative.mp. or exp Dentistry, Operative/
4. prosthesis, surgical dental.mp. or Dental Implants/
5. prostheses, surgical dental.mp. or exp Dental Implants/
6. surgical dental prosthesis.mp. or exp Dental Implants/
7. surgical dental prostheses.mp. or exp Dental Implants/
8. dental prosthesis, surgical.mp. or exp Dental Implants/
9. dental prostheses, surgical.mp. or exp Dental Implants/
10. implant, dental.mp. or exp Dental Implants/
11. dental implant.mp. or exp Dental Implants/
12. implants, dental.mp. or exp Dental Implants/
13. dental implants.mp. or exp Dental Implants/
14. procedures, maxillofacial.mp. or exp Oral Surgical Procedures/
15. procedure, maxillofacial.mp. or exp Oral Surgical Procedures/
16. maxillofacial procedure.mp. or exp Oral Surgical Procedures/
17. maxillofacial procedures.mp. or exp Oral Surgical Procedures/
18. exodontics.mp. or exp Surgery, Oral/
19. procedure, oral surgical.mp. or exp Oral Surgical Procedures/
20. oral surgical procedure.mp. or exp Oral Surgical Procedures/
21. surgical procedures, oral.mp. or exp Oral Surgical Procedures/
22. procedures, oral surgical.mp. or exp Oral Surgical Procedures/
23. surgical procedures, oral.mp. or exp Oral Surgical Procedures/
24. oral surgical procedures.mp. or exp Oral Surgical Procedures/
25. oral surgery.mp. or exp Surgery, Oral/
26. maxillofacial surgery.mp. or exp Surgery, Oral/
27. surgery,oral.mp. or exp Surgery, Oral/

28. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. benzodiazepinones.mp. or exp Benzodiazepinones/
30. Benzodiazepinones.mp. or exp Benzodiazepinones/
31. Alprazolam novopharm brand.mp. or exp Alprazolam/
32. novopharm brand of alprazolam.mp. or exp Alprazolam/
33. novo alprazol.mp. or exp Alprazolam/
34. novoalprazol.mp. or exp Alprazolam/
35. novo-alprazol.mp. or exp Alprazolam/
36. Alprazolam pfizer brand.mp. or exp Alprazolam/
37. pfizer brand of alprazolam.mp. or exp Alprazolam/
38. maleate, midazolam.mp. or exp Midazolam/
39. midazolam maleate.mp. or exp Midazolam/
40. midazolam.mp. or exp Midazolam/
41. effect, antianxiety.mp. or exp Anti-Anxiety Agents/
42. antianxiety effect.mp. or exp Anti-Anxiety Agents/
43. effects, anti-anxiety.mp. or exp Anti-Anxiety Agents/
44. anti anxiety effects.mp. or exp Anti-Anxiety Agents/
45. anti-anxiety effects.mp. or exp Anti-Anxiety Agents/
46. effect, anxiolytic.mp. or exp Anti-Anxiety Agents/
47. anxiolytic effect.mp. or exp Anti-Anxiety Agents/
48. effects, antianxiety.mp. or exp Anti-Anxiety Agents/
49. antianxiety effects.mp. or exp Anti-Anxiety Agents/
50. effects, anxiolytic.mp. or exp Anti-Anxiety Agents/
51. anxiolytic effects.mp. or exp Anti-Anxiety Agents/
52. effect,anti-anxiety.mp. or exp Anti-Anxiety Agents/
53. anti anxiety effect.mp. or exp Anti-Anxiety Agents/
54. anti-anxiety effect.mp. or exp Anti-Anxiety Agents/
55. anxiolytics.mp. or exp Anti-Anxiety Agents/
56. drugs, anti-anxiety.mp. or exp Anti-Anxiety Agents/
57. anti anxiety drugs.mp. or exp Anti-Anxiety Agents/

58. anti-anxiety drugs.mp. or exp Anti-Anxiety Agents/
59. minor tranquillizing agents.mp. or exp Anti-Anxiety Agents/
60. agents, minor tranquillizing.mp. or exp Anti-Anxiety Agents/
61. minor tranquilizing agents.mp. or exp Anti-Anxiety Agents/
62. agents, minor tranquilizing.mp. or exp Anti-Anxiety Agents/
63. tranquilizing agents, minor.mp. or exp Anti-Anxiety Agents/
64. agents, anxiolytic.mp. or exp Anti-Anxiety Agents/
65. anxiolytic agents.mp. or exp Anti-Anxiety Agents/
66. anti anxiety agents.mp. or exp Anti-Anxiety Agents/
67. agents, anti-anxiety.mp. or exp Anti-Anxiety Agents/
68. anti-anxiety agents.mp. or exp Anti-Anxiety Agents/
69. **29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68**

70. 69 and 28

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review – **PAGE 1**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **NOT APPLICABLE**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number - **PAGE 5**
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author – **PAGE 1**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review – **PAGE 11**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments **NOT APPLICABLE**
Support:		
Sources	5a	Indicate sources of financial or other support for the review – **PAGE 11**
Sponsor	5b	Provide name for the review funder and/or sponsor - **NOT APPLICABLE**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **NOT APPLICABLE**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known – **PAGES 3, 4**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) – **PAGE 4**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review – **PAGE 5**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage – **PAGE 6**
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated - **PAGE 6**
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **PAGE 6**

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) **PAGES 6, 7**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators **PAGES 7, 8**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications **PAGES 8-10**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **PAGE 5**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis **PAGE 7**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **PAGES 8, 9**
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) **PAGES 8, 9**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **PAGE 10**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **PAGE 9**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting **PAGES 9, 10**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **PAGES 9, 10**

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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